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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

LY, CHEYNE D

ART UNIT PAPER NUMBER

1631

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

ifc

Office Action Summary

Application No.

09/580,380

Applicant(s)

GIBSON ET AL.

Examiner

Cheyne D. Ly

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5,8-14,21-24 and 75-82 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 5, 8-14, 21-24, and 75-82 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 13, 2004 has been entered.
2. Claims 1, 5, 8-14, 21-24, and 75-82 are examined on the merits.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 5, 8-14, 21-24, and 75-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 recites the limitation "said structures" in line 14. There is insufficient antecedent basis for this limitation in the claim. It is noted that line 1 recites "the tertiary structure" which does not provide antecedent support for the limitation directed to plurality of "structures." Is the antecedent basis for the limitation of "said structures" the three-dimensional conformations? The same issue is present in claim 8. Claims 5, 9-14, 21-24, and 75-77 are rejected for being dependent from claim 1 or 8.

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6. Specific to claim 1, lines 12-15, the phrase “applying physical distance constraint information associated with the cross-linking...best fit the distance constraint information” causes the claim to be vague and indefinite because it is unclear what distance constraint information being used to fulfill the “best fit” criteria. For example, the instant specification (pages 12-17) discloses physical distance constraint information include techniques being used, crosslinkers, amino acid functionalities, etc. However, the claim encompasses any type of distance constraint information. Therefore, the vague and indefiniteness issue is caused by the undefined metes and bounds as applied to the criteria used to fulfill the “best fit” criteria. Clarification of the metes and bounds is required. The same issue is present in claims 5, 8, 21, and 78. Claims 2, 9-14, 22-24, 75-77, and 79-82 are rejected for being dependent from claim 8 or 78.

RESPONSE TO ARGUMENTS

7. On page 11, Applicant argues that the pending claims have been amended to explicitly recite that “distance constraint information associated with the cross-linking.” Therefore, the person of skill in the art will know what type of physical/chemical cross-link was used in the process. Applicant’s argument has been found to be unpersuasive. As noted above, the claims encompass any type of distance constraint information. For example, the instant specification (pages 12-17) discloses physical distance constraint information include techniques being used, crosslinkers, amino acid functionalities, etc. The claims have not been rejected because the limitation of “physical distance constraint information” is broad. However, due to the limitation of “physical distance constraint information” being broad, the metes and bounds of said claim

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have not been defined as directed to the criteria being used to fulfill the “best fit” criteria which necessitate the instant rejection.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 77-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. NEW MATTER REJECTION.

10. Claim 77, line 3, recites the limitation of “about 2-5 Angstroms”, while the pointed to supported, filed December 15, 2003, on page 29, lines 19-25, discloses “a moderate resolution structure (2-5A).” It is noted that the specific disclosure in the instant specification does not provide written description basis for the broad limitation of “about 2-5 Angstroms”. The same issue is present in claim 79.

11. Claim 78, line 4, recites the limitation of “at least about 10%”, while the pointed to supported, filed December 15, 2003, on page 25, discloses “about 10% of the number of amino acid residues.” It is noted that the specific disclosure in the instant specification does not provide

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written description basis for the more limited limitation of “at least about 10%.” Claims 79-82 are rejected for being dependent from claim 78.

CLAIM REJECTIONS - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

13. A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 5, 8, 14, 21-23, and 75-77 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lacroix et al. (1997).

RESPONSE TO ARGUMENT

15. On page 7-8, Applicant argues that Lacroix et al. does not disclose the limitation “applying physical distance constraint information associated with the cross-linking...to the candidate three-dimensional conformations...that best fit the distance constraint.” Applicant’s argument has been fully considered and found to be unpersuasive. Lacroix et al. discloses the “complementary information provided by chemical cross-linking and homology modeling studies was used to construct a three-dimensional model of the y-B mono, in which module V interacts with the serine protease on the side opposite to both the active site and the Arg446-Ile447 activation site” (Abstract etc.). The peptides are constrained as to the distance between Gly280 – Met351 from the N-terminus (Figure 5) and the sequence are determined by Edman degradation (Figure 7). The citation above is consistent with the required limitation of “applying physical distance constraint information...to the candidate three-dimensional conformations...”

16. Applicant argues that Lacroix et al. does not apply physical distance constraint information for identified cross-link fragments to choose a three-dimensional structure from among these multiple structures. Applicant's argument is not persuasive because the argued limitation is not present in the instant claims.

17. Specific to the argument that "the cited references do not propose a set of candidate three-dimensional conformations...that best fit the distance constraint information", due to the vague and indefiniteness of the "best fit" limitation as discussed above, the disclosure of Lacroix et al. is consistent with the require limitation.

18. On pages 8-9, Applicant argues that "the cited references do not propose a set of candidate three-dimensional conformations (for the protein's primary sequence) and then select from this set...that best fit the distance constraint information (associated with the cross-linking)." Applicant's argument has been found to be unpersuasive because Lacroix et al. discloses "all coordinates were obtained from the Protein Data Bank" (page 6272, column 1, last paragraph) which is consistent with the disclosure of primary sequence on page 27, lines 1-5. Due to the vague and indefiniteness of the "best fit" limitation as discussed above, the disclosure of Lacroix et al. is consistent with the require limitation.

19. Further, Applicant argues that the "cross-link information is not supplied to candidate three-dimensional conformations" has been found to be unpersuasive. The cited disclosure of

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“complementary information provided by chemical cross-linking and homology modeling studies was used to construct a three-dimensional model of the y-B mono, in which module V interacts with the serine protease on the side opposite to both the active site and the Arg446-Ile447 activation site” (Abstract etc.) is consistent with the argued limitation.

20. On page 10, Applicant argues that Figure 5 shows only two cross-links. Applicant’s argument has been found to be persuasive. Therefore, claims 78-82 have been withdrawn from the instant rejection.

BASIS FOR REJECTION

21. Lacroix et al. discloses the “complementary information provided by chemical cross-linking and homology modeling studies was used to construct a three-dimensional model of the y-B mono, in which module V interacts with the serine protease on the side opposite to both the active site and the Arg446-Ile447 activation site” (Abstract etc.). The peptides are constrained as to the distance between Gly280 – Met351 from the N-terminus (Figure 5) and the sequence are determined by Edman degradation (Figure 7). Lacroix et al. discloses “all coordinates were obtained from the Protein Data Bank” (page 6272, column 1, last paragraph) which is consistent with the disclosure of primary sequence on page 27, lines 1-5, of the instant specification, as in instant claim 1, lines 1-4 and 10-15.

22. Lacroix et al. discloses a method for three-dimensional modeling based on chemical cross-linking and homology modeling (page 6272, column 1, Computer-Assisted Three-

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dimensional Homology Modeling §) wherein the EDC cross-linked protein isolated and fragmented by proteolysis (Abstract et al.). The fragmented peptides are identified by mass spectrometry (page 6272, Mass Spectrometry Analysis §), as in instant claim 1, lines 5-9, and claim 5.

23. EDC is a reagent able to convert ionic bonds between carboxyl and amino groups into covalent pseudopeptide bonds (page 6271, column 1, lines 29-32), as in instant claim 8, lines 1-4.

24. The cross-linked species are isolated by dialysis and fractionation of autolytically cleaved Clr fragment (page 6271, column 2, lines 10-36), which represents a type of enriching reaction, as instant claim 8, lines 5-7.

25. The fragmented peptides are identified by mass spectrometry (page 6272, Mass Spectrometry Analysis §), as in instant claim 8, lines 8-11.

26. The program O has been used to build homology-based three-dimensional models of the protein modules of the Clr y-B segment and to assembly the modules interactively on the basis of the information yielded by chemical cross-linking (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling section), as in instant claim 8, lines 12-13.

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27. Lacroix et al. discloses the “complementary information provided by chemical cross-linking and homology modeling studies was used to construct a three-dimensional model of the y-B mono, in which module V interacts with the serine protease on the side opposite to both the active site and the Arg446-Ile447 activation site” (Abstract etc.). The peptides are constrained as to the distance between Gly280 – Met351 from the N-terminus (Figure 5) and the sequence are determined by Edman degradation (Figure 7), as in instant claim 8, lines 14-17, and claim 21.

28. Crossed linked fragment are enriched by fractionation of the reaction mixtures and isolation the cross-linked peptides via chromatography columns (page 6271, column 2, Isolation of the cross-linked peptides section) which is consistent with the disclosure of crosslink enrichment by intermolecular crosslink removal disclosed on pages 17-19 of the instant specification, as in instant claim 14.

29. The virtual library of proteolyzed products is represented by Table 1, which consists of average mass data (Table 1 and page 6274, column 1, lines 18-24), as in instant claim 22.

30. The hypothetical structures of the peptides with the predicted protein folds are illustrated in Figures 9-11. Further, Lacroix et al. discloses the homology modeling is similar to that of Rossi et al. 1995 (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling §). Rossi et al. discloses “threading” wherein a set of homologous three-dimensional structures is used as a reference template, sequence of proteins are aligned and the candidate structure is identified by comparing the said structure to the reference set (Rossi et al., page

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7313, Computer-Assisted Three-dimensional Homology Modeling §, columns 1-2), as in instant claims 23, 75, and 76.

31. The residues are superimposed within the limit of 1.5A (page 6277, column 1, lines 18-26), which is consistent of the broad limitation of about 2-5 Angstroms, as in instant claim 77.

CLAIM REJECTIONS - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

33. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

34. Claims 1, 5, 8-14, 21-23, and 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lacroix et al. (1997) taken with Mitra et al. (1979).

RESPONSE TO ARGUMENTS

35. On pages 9-10, Applicants argue that amended claim 8 from which claims 9-13 depend has overcome the Lacroix reference as discussed in the Rejections Under 35 U.S.S. §102(b) arguments. Applicant's arguments to the Rejections Under 35 U.S.S. §102(b) have been fully considered and found to be unpersuasive as discussed above. The above response as directed to the Rejections Under 35 U.S.S. §102(b) is being applied to Applicant's argument to overcome the instant 35 U.S.C. 103(a) rejection.

36. Lacroix et al. (1997) describes the limitations of claims 1, 5, 8, 14, 21-23, and 75-77 as discussed above.

37. However, Lacroix et al. does not disclose the specific limitations of claims 9-13.

BASIS FOR REJECTION

38. Mitra et al. describes reagents such as cross-linking reagents have wide application to the studies protein structure and the said agents are important tools for biochemist and molecular biologists for protein structure determination (page 3110, column 1, lines 22-30). Mitra et al. suggests that cross-linking reagents are applicable and important tools to determining the tertiary structure of proteins such as the Clr serine protease of Lacroix et al. Mitra et al. establishes a prima facie case that it would have been obvious to one of ordinary skill in the art at the time of the instant to apply the cross-linking reagents of Mitra et al. to the cross-linking method of Lacroix et al.

39. Mitra et al. describes the general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction §, lines 1-4) such as bifunctional reagents (page 3106, column 2, Discussion §, lines 12-13) which reaction with amines (page 3100, column 1, lines 64-65) as in instant claims 9 and 10.

40. Two reagents are synthesized wherein one reactions with a nuclease between lysine residues 7 and 37 and the other at 31 and 41 (Abstract etc.), as in instant claims 11 and 12.

41. The first cross-link is introduced to allow a new conformation for the second link to take place (page 3108, column 1, lines 9-12), as in instant claim 13. It is noted that the first cross-link reaction is optimized to introduce one cross-linker per molecule before the second cross-linker can be introduced.

42. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Mitra et al. for general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction §, lines 1-4) to use the method Lacroix et al. for determining the tertiary structure of a protein with the cross-linking reagents of Mitra et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for three-dimensional modeling based on chemical cross-linking and homology modeling as taught by Lacroix et al. and use the said method with the cross-linker reagents as taught Mitra et al.

CONCLUSION

43. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. The USPTO's official fax number is (571) 273-8300.

44. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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45. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

46. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

47. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

C. Dune Ly
3/7/05

Ardin H. Marschel 3/7/05
ARDIN H. MARSCHEL
PRIMARY EXAMINER